GAMMA AMINO BUTYRIC ACID ANALOGS AND OPTICAL ISOMERS

CROSS-REFERENCE TO RELATED APPLICATIONS

This is a continuation of application Ser. No. 08/064,285 filed on May 18, 1993, now abandoned; which application is a continuation-in-part of application U.S. Ser. No. 07/886,080, filed May 20, 1992, now abandoned, which is a continuation-in-part of application U.S. Ser. No. 07/618,692, filed Nov. 27, 1990, now abandoned.

GRANT REFERENCE

The research carried out in connection with this invention was supported in part by a grant from the National Institutes of Health. The U.S. Government has certain rights in this invention.

The present invention relates to novel compounds that are analogs of glutamic acid and gamma-aminobutyric acid (GABA). More specifically, the analogs are useful as anti-seizure therapy for central nervous system disorders such as epilepsy, Huntington's chorea, cerebral ischemia, Parkinson's disease, tardive dyskinesia, and spasticity. It is also possible that the present invention could be used as an antidepressant, anxiolytic, and antipsychotic activity.

BACKGROUND OF THE INVENTION

Gamma aminobutyric acid (GABA) and glutamic acid are two major neurotransmitters involved in the regulation of brain neuronal activity. GABA is the major inhibitory neurotransmitter and L-glutamic acid is an excitatory transmitter (Roberts E, et al, *GABA in Nervous System Function,* Raven Press: New York, 1976; McGeer E G, et al, *Glutamine, Glutamate, and GABA in the Central Nervous System;* Hertz L, Kvamme E, McGeer E G, Schousbal A, eds., Liss: New York, 1983;3–17). An imbalance in the concentration of these neurotransmitters can lead to convulsive states. Accordingly, it is clinically relevant to be able to control convulsive states by controlling the metabolism of this neurotransmitter. When the concentration of GABA diminishes below a threshold level in the brain, convulsions result (Karlsson A, et al, *Biochem. Pharmacol* 1974;23:3053–3061). When the GABA levels rise in the brain during convulsions, seizures terminate (Hayashi T J, *Physiol.* (London) 1959;145:570–578). The term seizure as used herein means excessive unsynchronized neuronal activity that disrupts normal neuronal function. In several seizure disorders there is concomitant with reduced brain GABA levels a diminished level of L-glutamic acid decarboxylase (GAD) activity also observed (McGeer P O, et al, In: *GABA in Nervous System Function;* Roberts E, Chase T N, Tower D B, eds., Raven Press: New York 1976:487–495; Butterworth J, et al, *Neurochem.* 1983;41:440–447; Spokes E G, *Adv. Exp. Med. Biol.* 1978;123:461–473; Wu J Y, et al, *Neurochem. Res.* 1979;4:575–586; and Iversen L L, et al, *Psychiat. Res.* 1974;11:255–256). Often, the concentrations of GAD and GABA vary in parallel because decreased GAD concentration results in lower GABA production.

Because of the importance of GABA as an inhibitory neurotransmitter, and its effect on convulsive states and other motor dysfunctions, a variety of approaches have been taken to increase the brain GABA concentration. For example, the most obvious approach was to administer GABA. When GABA is injected into the brain of a convulsing animal, the convulsions cease (Purpura D P, et al, *Neurochem.* 1959;3:238–268). However, if GABA is administered systematically, there is no anticonvulsant effect because GABA, under normal circumstances, cannot cross the blood brain barrier (Meldrum B S, et al, *Epilepsy;* Harris P, Mawdsley C, eds., Churchill Livingston: Edinburg 1974:55. In view of this limitation, there are three alternative approaches that can be taken to raise GABA levels.

The most frequent approach is to design a compound that crosses the blood brain barrier and then inactivates GABA aminotransferase. The effect is to block the degradation of GABA and thereby increase its concentration. Numerous mechanism-based inactivators of GABA aminotransferase are known (Silverman R B, *Mechanism-Based Enzyme Inactivation: Chemistry and Enzymology,* Vol. I and Il, CRC: Boca Raton 1988).

Another approach is to increase GABA concentrations in the brain by making GABA lipophilic by conversion to hydrophobic GABA amides (Kaplan J P, et al, *G.J. Med. Chem.* 1980;23:702–704; Carvajal G, et al, *Biochem. Pharmacol.* 1964;13:1059–1069; Imines: Kaplan J P, Ibid.; or GABA esters: Shashoua V E, et al, *J. Med. Chem.* 1984;27:659–664; and PCT Patent Application WO85/00520, published Feb. 14, 1985) so that GABA can cross the blood brain barrier. Once inside the brain, these compounds require amidase and esterases to hydrolyze off the carrier group and release GABA.

Yet another approach is to increase 25 brain GABA levels by designing an activator of GAD. A few compounds have been described as activators of GAD. The anticonvulsant agent, maleicimid, was reported to increase the activity of GAD by 11% and as a result increase GABA concentration in the substantia nigra by up to 38% (Janssens de Varebeke P, et al, *Biochem. Pharmacol.* 1983;32:2751–2755. The anticonvulsant drug sodium valproate (Loscher W, *Biochem. Pharmacol.* 1982;31:837–842; Phillips N I, et al, *Biochem. Pharmacol.* 1982;31:2257–2261) was also reported to activate GAD and increase GABA levels.

The compounds of the present invention have been found to activate GAD in vitro and have a dose dependent protective effect on-seizure in vivo.

Also, the compounds of the present invention have been found to bind a novel binding site which was identified to bind tritiated gabapentin. Gabapentin has been found to be an effective treatment for the prevention of partial seizures in patients refractory to other anticonvulsant agents. Chadwick D, Gabapentin, pp. 211–222, In: *Recent Advances in Epilepsy,* Vol. 5, Pedley T A, Meldrum B S, (eds.) Churchill Livingstone, New York (1991). The novel binding site labeled by tritiated gabapentin was described in membrane fractions from rat brain tissue and in autoradiographic studies in rat brain sections, Hill D, Ibid. This binding site has been used to evaluate the compounds of the present invention.

The novel compounds of the present invention are set forth below as Formula I. It should be noted that the compound of Formula I wherein R_1 is methyl and each of R_2 and R_3 is hydrogen is taught in Japan Patent Number 49-40460.